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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/975,650	10/11/2001	Sui-Po Zhang	ORT-1518	8659

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EXAMINER	
ULM, JOHN D	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 07/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/975,650	Zhang et al.
Examiner	**Art Unit**
John Ulm	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-18 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-18 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4, 5
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1) Claims 1 to 18 are pending in the instant application.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2) Claims 1 to 18 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. An invention which lacks an element that is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

2.1) As stated in the "SUMMARY OF THE INVENTION' on page 2 of the specification, the instant invention is based upon Applicant's discovery that the human vanilloid receptor hVR-1 has an increased binding affinity for certain ligands, such as resiniferatoxin, capsaicin and capsazepine, at a pH of 8.0 or greater. This property is unexpected in view of the Szallas et al. publication (Naunyn-Schmiedeberg's Archives of Pharmacology 347:84-91(1993), which employed essentially the same experimental binding protocol as Applicant and disclosed that ligand binding to a rat vanilloid receptor "was reduced by 50% at pH 8.0 and by 70% at pH 9.0" relative to binding at pH 7.4 or lower. One to whom this art pertains would not reasonable conclude that Applicant's discovery is applicable to vanilloid receptors other than hVR-1 simply because the evidence of record shows that vanilloid receptors from different mammals are not predictive of one another as demonstrated by Applicant's unexpected results. This position is further supported by the statement on page 85 of Szallas et al. that "it is complicated

extrapolating to humans since in animals capsaicin shows striking species-related differences in action". Therefore, one does not have a reasonable expectation that a vanilloid receptor other than hVR-1 will respond to alkaline pH in the manner discovered by Applicant.

2.2) Further, it is unclear if the results reported in the instant specification are comparable to those of Szallas et al. because Applicant included alpha$_1$-acid glycoprotein (AGP) in their experimental protocol (lines 24 and 25 on page 9 of the instant specification) whereas the text on page 88 of Szallas et al. stated that "the effect of pH (5.5-9.0) on specific [^{3}H]RTX binding has been examined in our standard filtration assay without AGP". Based upon the evidence of record one of ordinary skill could not determine if the unexpected results observed by Applicant are a reflection of differences between rat and human VR-1 or if they resulted from the inclusion of AGP by Applicant and its exclusion by Szallas et al. Therefore, the skilled artisan does not have a reasonable expectation of practicing a method which achieves Applicant's unexpected results without employing the critical combination of hVR-1 and AGP at a pH of about 8.0 or greater.

2.3) Two additional ingredients which appear to be critical to a binding assay of the instant invention are $MgCl_2$ at a concentration of 2 mM and $CaCl_2$ at a concentration of 0.75 nM. Whereas the instant specification and a number of references of record describe **binding** assays which employ vanilloid receptors, there does not appear to be a single reference of record which describes a vanilloid receptor ligand binding assay lacking these two compounds and in which ligand binding by the receptor was not reduced, impaired or abolished. The inclusion of these two

compounds in any reaction mixture that is to be employed in a binding assay of the instant invention appears to be critical to the functionality of the vanilloid receptor employed therein.

2.4) Claims 1 and 3 to 16 encompass an assay which employs "at least a ligand-interacting portion of a vanilloid receptor protein". Neither the instant specification nor the art of record provides a description of, or the guidance needed to make a functional vanilloid receptor protein having anything than its entire native amino acid sequence. It is well established in the art that VR-1 is an integral membrane channel protein having a complex three-dimensional structure comprising six putative transmembrane domains and a multiple extracellular and cytoplasmic domains. It is also well known in the art that integral membrane channels are usually composed of proteins or protein complexes having a total of not less than twelve transmembrane domains. Therefore, one of ordinary skill would reasonably believe that VR-1 probably functions in at least a dimeric form. Given the complex structure of VR-1 and the complete absence of any information with respect to the identity of those minimal portions of VR-1 which are essential for ligand binding, an artisan can not produce a ligand-interacting portion of a vanilloid receptor protein without the need to resort to the substantial amount of undue experimentation that would be required to identify those critical portions of VR-1 which are needed to produce the protein required by these claims. A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that:

"[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one can not following the guidance presented therein and practice the claimed method without first making a substantial inventive contribution.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3) Claims 1 to 18 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The method, as claimed, requires a comparison step and the limitation "determining if the test compound bound to the receptor by observing a reduction in the amount of expected labeled ligand" is insufficient to provide this element. The term "a reduction in the amount of expected labeled ligand" is a relative term which requires a point of reference and none is given.

4) Claims 2 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is vague and indefinite in requiring a "portion" of a receptor protein to be an "intact" receptor protein. The term "portion" is defined in the dictionary as "an often limited part set off or abstracted from a whole". It is unclear how a receptor protein can be a portion of itself.

Claim 4 is incorrect because of the presence of the term "1wherein" which should be "1 wherein".

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5) Claims 1 to 3 and 6 to 16 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by the Szallasi et al. publication (Neuroscience Letters 165:101-104, 1994, cited by Applicant). Table 1 on page 103 of the Szallasi et al. publication described the results of a binding assay which expressly met all of the limitations of the instant claims. That binding assay was performed at a pH of 7.4, which is "about 7.5", and included 2 mM $MgCl_2$, 0.75 nM $CaCl_2$, AGP, labeled RTX, a test compound, a recovery step and a comparative step.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm whose telephone number is (703) 308-4008. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242 or (703) 872-9306. Official responses under 37 C.F.R. § 1.116 should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JOHN ULM
PRIMARY EXAMINER
GROUP 1800